Poster **268**

Response rates with zilucoplan among patients with generalized myasthenia gravis in an interim analysis of RAISE-XT, a Phase 3 open-label extension study

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Introduction

- Complement-mediated architectural destruction of the NMJ by pathogenic autoantibodies is a major mechanism involved in gMG pathology[1,2]
- Zilucoplan is a small peptide C5 inhibitor with a dual mechanism of action: it prevents C5 cleavage to C5a and C5b and hinders the formation of C5b6, should any C5b be formed, thereby preventing activation of the terminal complement pathway and formation of the MAC[3,4]
- Zilucoplan showed clinically meaningful and statistically significant improvements in MG-specific outcomes in patients with AChR+ gMG in Phase 2[5] and Phase 3 (RAISE)[4] randomized, placebo-controlled studies
- Long-term data will enhance our understanding of the safety and efficacy of zilucoplan in patients with gMG

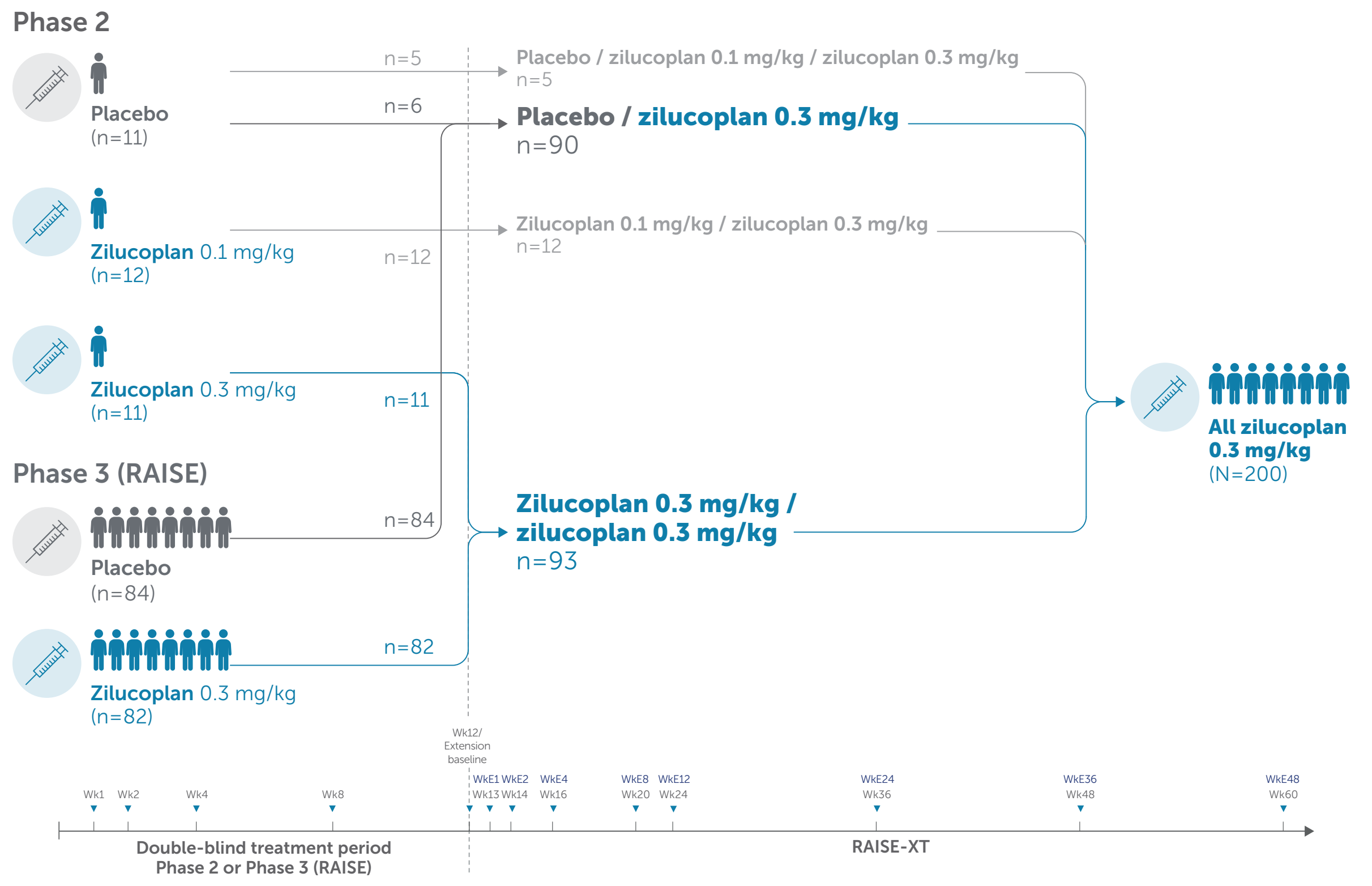
Methods

- RAISE-XT (NCT04225871) is an ongoing, Phase 3, multicenter, open-label extension study
- Adults with gMG who completed a qualifying zilucoplan study (Phase 2, NCT03315130; or Phase 3, NCT04115293 [RAISE]) self-administered daily subcutaneous injections of zilucoplan 0.3 mg/kg (**Figure 1**)
- The primary outcome was incidence of TEAEs
- Here, we report the change from double-blind study baseline to Week 60 (Extension Week 48) in MG-ADL score; proportion of MG-ADL and QMG responders (defined by reduction of ≥3 points and ≥5 points without rescue therapy, respectively) up to Week 60; and proportion of patients who achieved MSE (MG-ADL score of 0 or 1) up to Week 60

Results

- In total, 200 patients enrolled in RAISE-XT (**Table 1**)
- Median exposure was 1.2 years at data cut-off (September 8, 2022; range 0.11–4.45 years)
- TEAEs occurred in 188 (94%) patients; the most common TEAEs were worsening of MG, and COVID-19 (**Table 2**)
- Compared to double-blind baseline, MG-ADL scores continued to improve through to Week 24 and were sustained through to Week 60 for the zilucoplan group (**Figure 2**)
  - Rapid improvements in MG-ADL scores were observed in the placebo-switch group within one week of switching to zilucoplan
  - These results were mirrored in QMG, MGC and MG-QoL 15r scores (data not shown)
- The responder rates for MG-ADL, QMG and MSE increased to Week 24 and were sustained through to Week 60 in the zilucoplan group (**Figure 3**)
  - The placebo-switch group experienced a rapid increase in responder rates within one week after switching to zilucoplan

Figure 1 RAISE-XT study design



Efficacy data for the zilucoplan 0.1 mg/kg treatment groups are not presented because, due to the small number of participants in each group, no meaningful conclusions can be drawn. These patients are included in the 'all zilucoplan' group.

Table 1 Patient demographics and baseline disease characteristics at RAISE-XT baseline

		Placebo/ zilucoplan 0.3 mg/kg (n=90)	Zilucoplan 0.3 mg/kg/ 0.3 mg/kg (n=93)	All zilucoplan (N=200)
	Age, years, mean (SD)	**53.7** (15.5)	**52.9** (14.5)	**53.3** (15.0)
	Sex, male, n (%)	**42** (46.7)	**41** (44.1)	**90** (45.0)
MGFA Disease Class, n (%)	II (IIa, IIb)	**29** (32.2)	**25** (26.9)	**59** (29.5)
	III (IIIa, IIIb)	**57** (63.3)	**60** (64.5)	**129** (64.5)
	IV (IVa, IVb)	**4** (4.4)	**8** (8.6)	**12** (6.0)
	MG-ADL score, mean (SD)	**7.7** (4.5)	**5.2** (3.9)	**6.3** (4.3)
	QMG score, mean (SD)	**15.6** (6.0)	**12.5** (5.6)	**14.0** (5.9)
	Prior thymectomy, n (%)	**39** (43.3)	**49** (52.7)	**96** (48.0)
	Prior MG crisis, n (%)	**29** (32.2)	**30** (32.3)	**62** (31.0)
	Duration of disease, years, mean (SD)	**9.3** (10.5)	**9.4** (9.4)	**9.4** (9.7)
	Age at onset, years, mean (SD)	**44.0** (18.7)	**43.4** (17.6)	**43.6** (17.9)
Prior gMG-specific medication, n (%)	Corticosteroids	**77** (85.6)	**85** (91.4)	**177** (88.5)
	Immunosuppressants	**69** (76.7)	**64** (68.8)	**147** (73.5)
	Cholinesterase inhibitors	**86** (95.6)	**91** (97.8)	**194** (97.0)

ITT population.

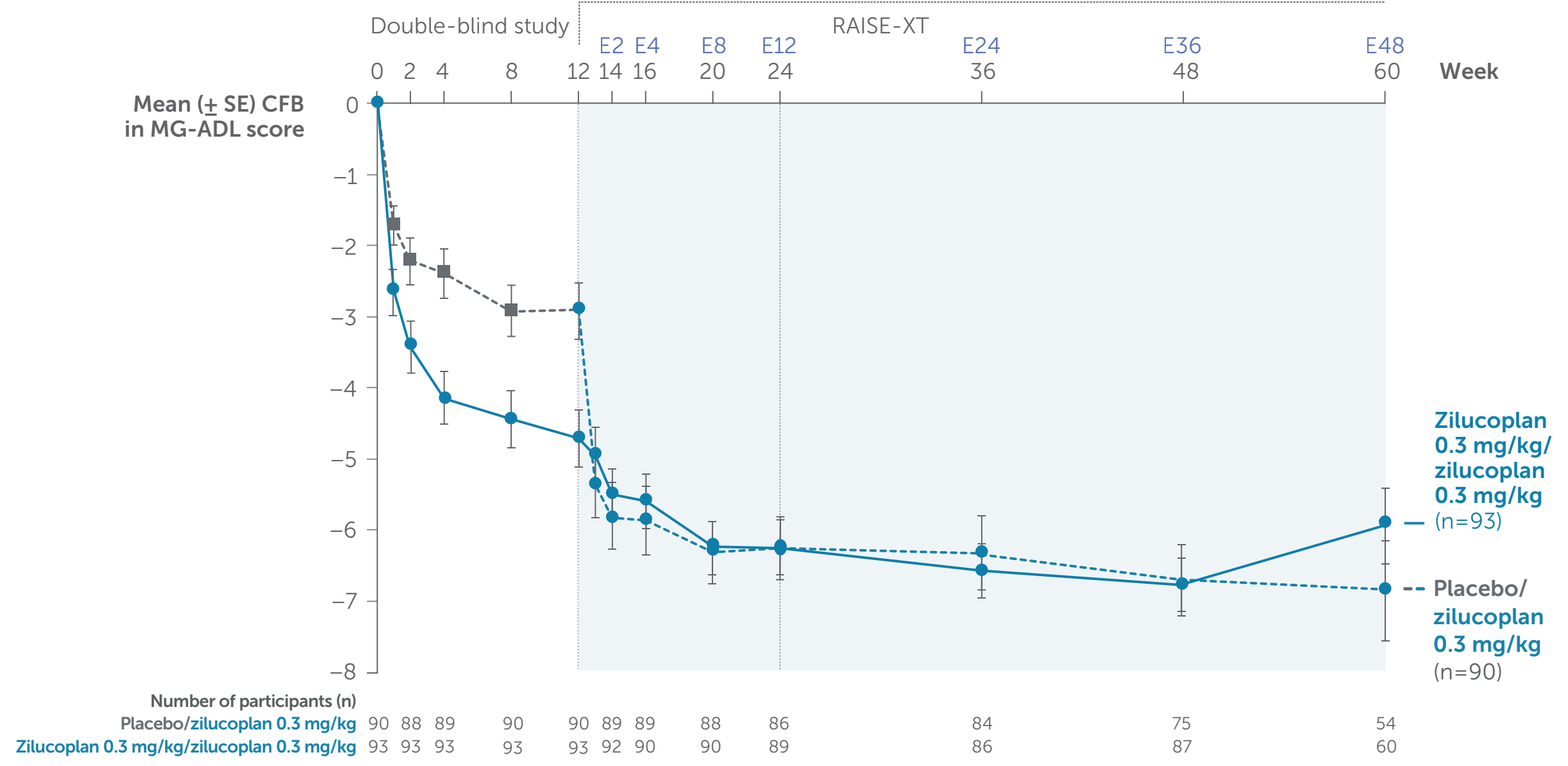
Baseline was defined as the last available assessment at the start of RAISE-XT.

Table 2 Overview of TEAEs

	Placebo/ zilucoplan 0.3 mg/kg (n=90) n (%)	Zilucoplan 0.3 mg/kg/ 0.3 mg/kg (n=93) n (%)	All zilucoplan (N=200) n (%)
Any TEAE	**86** (95.6)	**85** (91.4)	**188** (94.0)
Myasthenia gravis	**21** (23.3)	**24** (25.8)	**52** (26.0)
COVID-19	**20** (22.2)	**24** (25.8)	**49** (24.5)
Headache	**14** (15.6)	**15** (16.1)	**35** (17.5)
Diarrhea	**9** (10.0)	**17** (18.3)	**30** (15.0)
Nasopharyngitis	**10** (11.1)	**14** (15.1)	**30** (15.0)
Serious TEAE	**23** (25.6)	**34** (36.6)	**64** (32.0)
TEAE resulting in permanent withdrawal from IMP*	**10** (11.1)	**7** (7.5)	**17** (8.5)
Treatment-related TEAE	**32** (35.6)	**29** (31.2)	**67** (33.5)
Severe TEAE	**24** (26.7)	**25** (26.9)	**57** (28.5)
TEAEs leading to deaths	**1** (1.1)	**3** (3.2)	**4** (2.0)

Safety set. Only the most common TEAEs occurring in ≥15% of patients overall are reported.
*Includes deaths.
No deaths were considered treatment-related. TEAEs leading to death included cardiac arrest (n=2) and accidental head injury (n=1) in the zilucoplan 0.3 mg/kg/0.3 mg/kg group, and death from an unknown cause (n=1) in the placebo/zilucoplan 0.3 mg/kg group.

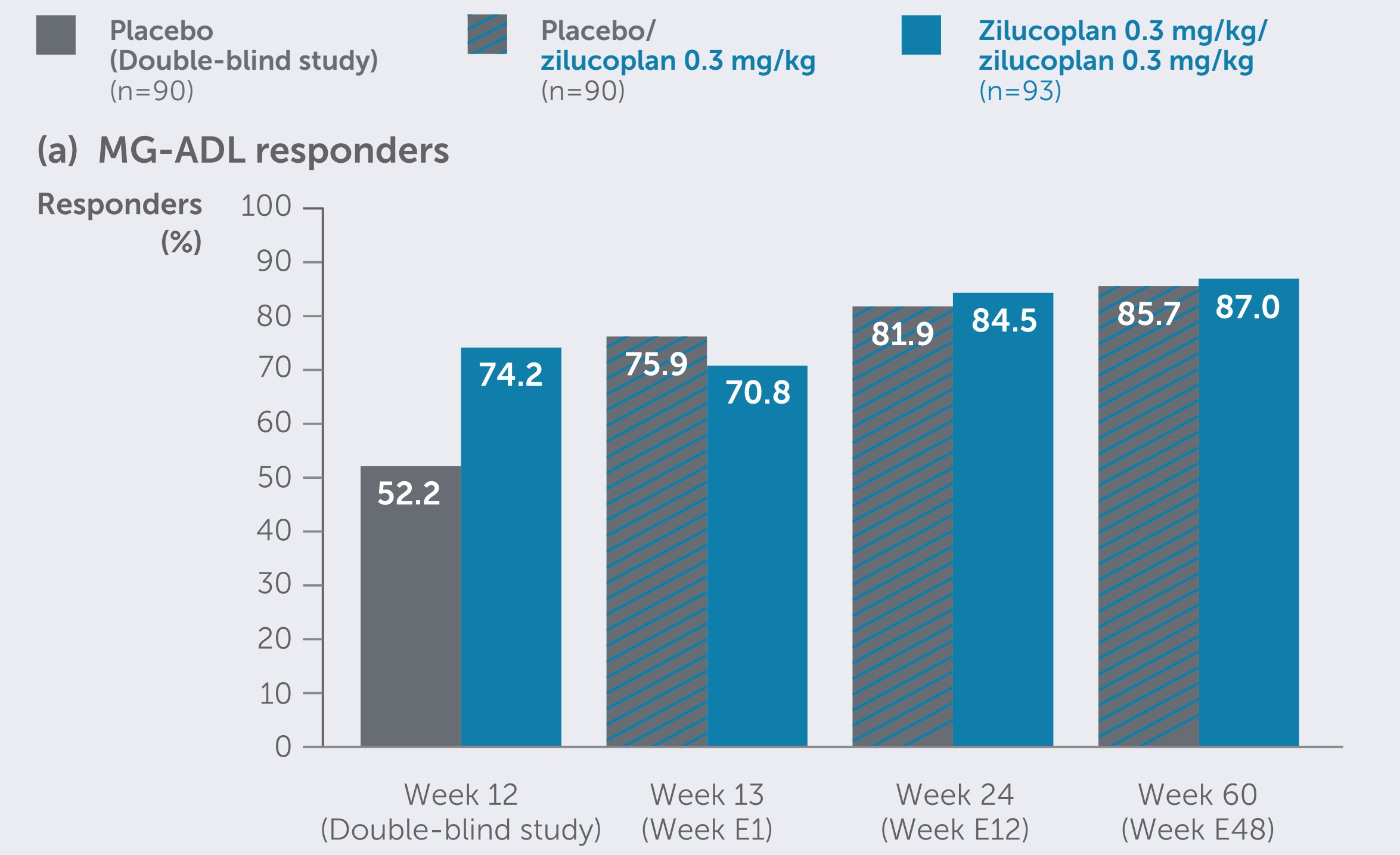
Figure 2 Mean CFB in MG-ADL score to Week 60



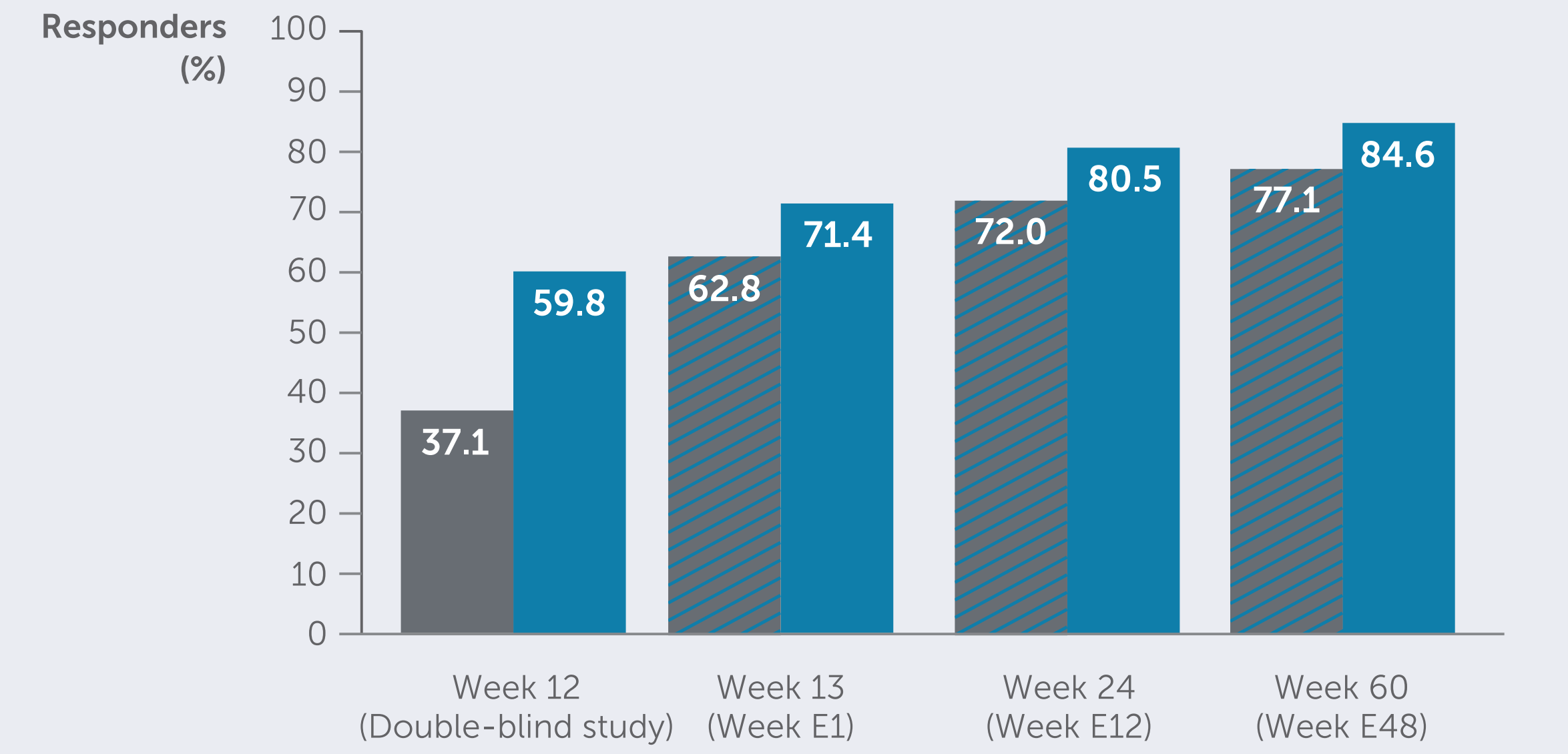
	LS mean (SE) CFB at Week 24	LS mean difference at Week 24 vs Week 12 (95% CI)
Placebo/zilucoplan 0.3 mg/kg	**−6.46** (0.87)	**−3.69** (−6.07, −1.30) p=0.0028
Zilucoplan 0.3 mg/kg/zilucoplan 0.3 mg/kg	**−6.06** (0.52)	**−1.52** (−2.60, −0.44) p=0.0062

mITT population. Changes from baseline in MG-ADL score were estimated using an MMRM ANCOVA with baseline score, baseline MG-ADL score, baseline QMG score, geographical region, parent study factor, and baseline score X visit (interaction term) as fixed effects and study participant as a random effect. The model included Week 1 to Week 12 (double-blind treatment period) and Week 13 to Week 60 (open-label extension period). An unstructured correlation structure was used.

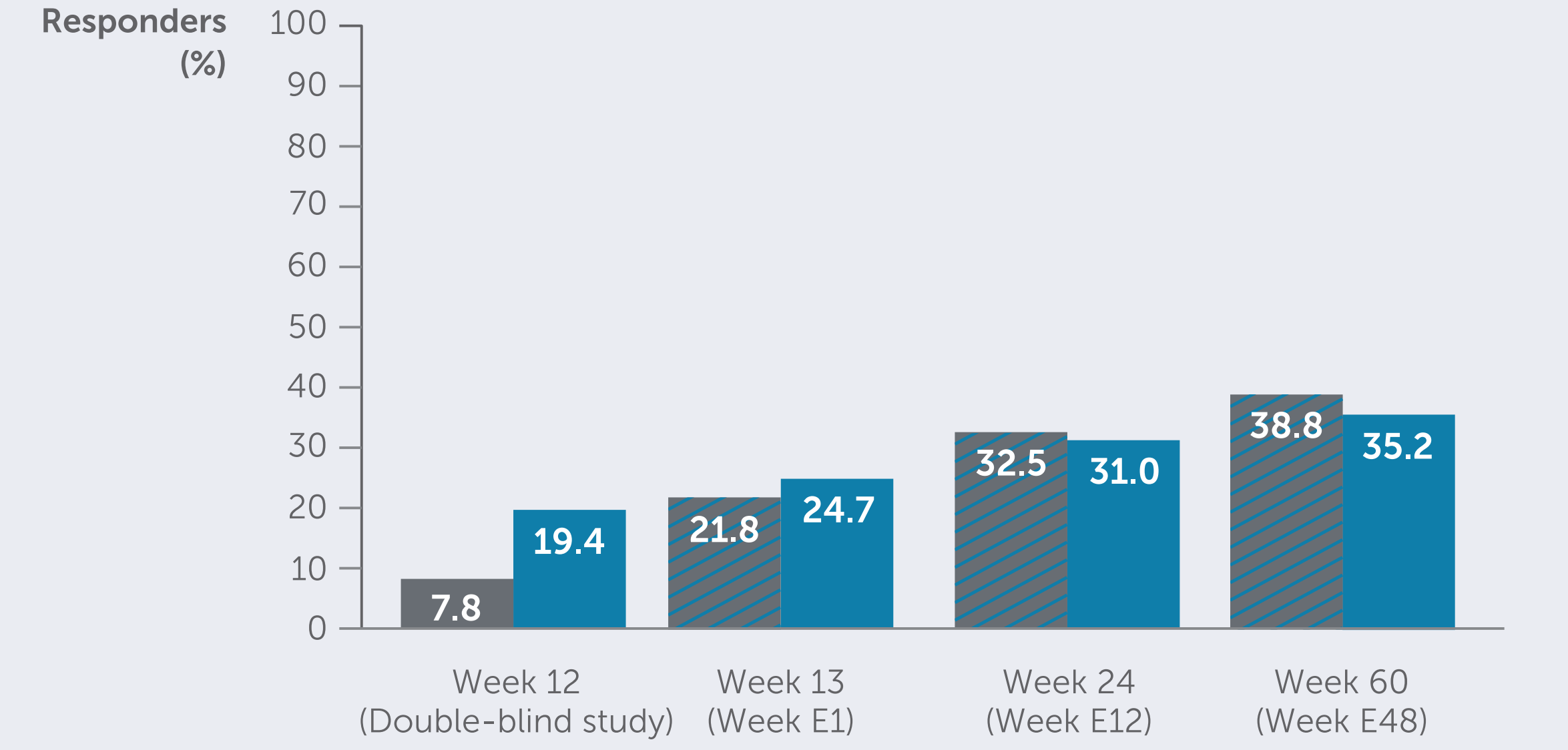
Figure 3 Responder rates for (a) MG-ADL, (b) QMG and (c) MSE at extension study baseline to Week 60



(b) QMG responders



(c) MSE responders



Summary and conclusions

This is an interim analysis of RAISE-XT, an open-label Phase 3 extension study to evaluate the long-term safety, tolerability and efficacy of the C5 complement inhibitor zilucoplan in patients with gMG

Zilucoplan demonstrated a favorable long-term safety profile and was well tolerated; no new safety concerns were identified compared with the qualifying double-blind studies

After 60 weeks of treatment with zilucoplan, approximately 87% and 85% of patients were MG-ADL and QMG responders, respectively, and more than 35% of patients achieved MSE

In the patients who switched from placebo to zilucoplan, rapid improvements were observed in MG-ADL, QMG and MSE response rates within one week of starting zilucoplan in the OLE, and were maintained up to Week 60

In this interim analysis of RAISE-XT, zilucoplan demonstrated a favorable long-term safety profile; efficacy was sustained over 60 weeks of treatment in a broad population of adult patients with AChR+ gMG

Abbreviations: AChR+, acetylcholine receptor autoantibody-positive; ANCOVA, analysis of covariance; C5(b), complement component 5(b); CFB, change from baseline; CI, confidence interval; COVID-19, coronavirus disease 2019; E, extension; (g)MG, (generalized) myasthenia gravis; IMP, investigational medicinal product; kDa, kiloDalton; LS, least squares; MAC, membrane attack complex; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QoL 15r, Myasthenia Gravis Quality of Life 15-item revised; (m)ITT, (modified) intention-to-treat; MMRM, mixed model repeated measures; MSE, minimal symptom expression; NMJ, neuromuscular junction; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; Wk, week; WkE, extension week.

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